

069/582863

PCT/SE00/00756

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE
in its capacity as elected Office

Date of mailing (day/month/year) 07 December 2000 (07.12.00)	
International application No. PCT/SE00/00756	Applicant's or agent's file reference H 2094-1 WO
International filing date (day/month/year) 19 April 2000 (19.04.00)	Priority date (day/month/year) 21 April 1999 (21.04.99)
Applicant GUSTAFSSON, David	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
01 November 2000 (01.11.00)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer A. Karkachi
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference A 2094-1 WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/SE00/00756	International filing date (day/month/year) 19.04.2000	Priority date (day/month/year) 21.04.1999
International Patent Classification (IPC) or national classification and IPC: A61K 38/55, A61K 38/06, A61P 9/14		
Applicant AstraZeneca AB et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 01.11.2000	Date of completion of this report 28.06.2001
Name and mailing address of the IPEA/SE Patent- och registreringsverket P.O. Box 5055 S-102 42 STOCKHOLM Facsimile No. 08-667 72 88	Authorized officer Carolina Gómez Lagerlöf/BS Telephone No. 08-782 25 00

Form PCT/IPEA/409 (cover sheet) (January 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

international application No.

PCT/SE00/00756

I. Basis of the report

1. With regard to the **elements** of the international application:*

- ☒ the international application as originally filed
- ☐ the description:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____
- ☐ the claims:
pages _____, as originally filed
pages _____, as amended (together with any statement) under article 19
pages _____, filed with the demand
pages _____, filed with the letter of _____
- ☐ the drawings:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____
- ☐ the sequence listing part of the description:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages _____
- ☐ the claims, Nos. _____
- ☐ the drawings, sheet/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2 (c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

** Any replacement sheet containing such amendments must be referred to under item I and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/SE00/00756

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 12-18

because:

☒ the said international application, or the said claims Nos. 12-18

relate to the following subject matter which does not require an international preliminary examination (*specify*):

See PCT Rule 67.1.(iv).: Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____ are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/SE00/00756

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	<u>1-11, 19</u>	YES
	Claims		NO
Inventive step (IS)	Claims	<u>1-11, 19</u>	YES
	Claims		NO
Industrial applicability (IA)	Claims	<u>1-11, 19</u>	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

The claims disclose a pharmaceutical formulation comprising a low molecular weight inhibitor and a prodrug of a low molecular weight inhibitor. The claims further disclose the use of the formulation.

The examination is based on the search that has been focused on melagatran and the term "thrombin inhibitor".

During the search the following documents were found:

A WO 9616671 A1 (Astra Aktiebolag), 6 June 1996

B WO 9723499 A1 (Astra Aktiebolag), 3 July 1997

C Throm Haemost, Vol 81, 1999, pp 358-363

D Journal of Thrombosis and Thrombolysis, Vol 6, 1998, pp 199-206

Document A shows the use of a pharmaceutical formulation containing melagatran for the treatment of thromboembolism.

Document B discloses prodrugs of thrombin inhibitors and their use.

Document C shows that melagatran can be used by patients suffering from deep vein thrombosis.

Document D shows that inogatran can be use in the treatment of deep venous thrombosis.

The documents do not mention a composition that contains both the thrombin inhibitor and a prodrug of a thrombin inhibitor.

Thus, claims 1-11 and 19 are considered to fulfil the requirements of novelty, inventive step and industrial applicability.

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : A61K 38/55, 38/06, A61P 9/14	A1	(11) International Publication Number: WO 00/64470 (43) International Publication Date: 2 November 2000 (02.11.00)
(21) International Application Number: PCT/SE00/00756 (22) International Filing Date: 19 April 2000 (19.04.00) (30) Priority Data: 9901442-5 21 April 1999 (21.04.99) SE 9904419-0 3 December 1999 (03.12.99) SE (71) Applicant (for all designated States except US): AS-TRAZENECA AB [SE/SE]; S-151 85 Södertälje (SE). (72) Inventor; and (75) Inventor/Applicant (for US only): GUSTAFSSON, David [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE). (74) Agent: ASTRAZENECA AB; Global Intellectual Property, Patents, S-151 85 Södertälje (SE).		(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: A PHARMACEUTICAL FORMULATION COMPRISING A LOW MOLECULAR WEIGHT THROMBIN INHIBITOR AND ITS PRODRUG (57) Abstract According to the invention there is provided a kit of parts comprising: (a) a pharmaceutical formulation including a low molecular weight thrombin inhibitor, or a pharmaceutically acceptable derivative thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier; and (b) a pharmaceutical formulation including a prodrug of a low molecular weight thrombin inhibitor, or a pharmaceutically acceptable derivative of that prodrug, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier, which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other, as well as the use of such a kit of parts in the treatment of a condition in which inhibition of thrombin is required or desired.		

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A PHARMACEUTICAL FORMULATION COMPRISING A LOW MOLECULAR
WEIGHT THROMBIN INHIBITOR AND ITS PRODRUG.

Field of the Invention

- 5 This invention relates to a new use of low molecular weight thrombin inhibitors.

Background and Prior Art

- 10 Blood coagulation is the key process involved in both haemostasis (i.e. the prevention of blood loss from a damaged vessel) and thrombosis (i.e. the formation of a blood clot in a blood vessel, sometimes leading to vessel obstruction).
- 15 Coagulation is the result of a complex series of enzymatic reactions. One of the ultimate steps in this series of reactions is the conversion of the proenzyme prothrombin to the active enzyme thrombin.

- Thrombin is known to play a central role in coagulation. It activates
- 20 platelets, leading to platelet aggregation, converts fibrinogen into fibrin monomers, which polymerise spontaneously into fibrin polymers, and activates factor XIII, which in turn crosslinks the polymers to form insoluble fibrin. Furthermore, thrombin activates factor V and factor VIII leading to a "positive feedback" generation of thrombin from
- 25 prothrombin.

Effective inhibitors of thrombin are thus known, and/or are expected, to be useful as anticoagulants and therefore useful in the therapeutic treatment of thrombosis and related disorders.

- 5 The early development of low molecular weight inhibitors of thrombin has been described by Claesson in Blood Coagul. Fibrinol. (1994) 5, 411. Low molecular weight thrombin inhibitors have been described more recently in US Patent N° 4,346,078; International Patent Applications WO 93/11152, WO 93/18060, WO 93/05069, WO 94/20467, WO 94/29336,
10 WO 95/35309, WO 95/23609, WO 96/03374, WO 96/06832, WO 96/06849, WO 96/25426, WO 96/32110, WO 97/01338, WO 97/02284, WO 97/15190, WO 97/30708, WO 97/40024, WO 97/46577, WO 98/06740, WO 97/49404, WO 97/11693, WO 97/24135, WO 97/47299, WO 98/01422, WO 98/57932, WO 99/29664, WO 98/06741, WO
15 99/37668, WO 99/37611, WO 98/37075, WO 99/00371, WO 99/28297, WO 99/29670, WO 99/40072, WO 99/54313, WO 96/31504, WO 00/01704 and WO 00/08014; and European Patent Applications 648 780, 468 231, 559 046, 641 779, 185 390, 526 877, 542 525, 195 212, 362 002, 364 344, 530 167, 293 881, 686 642, 669 317, 601 459 and 623 596.

20

- In particular, international patent application WO 94/29336 discloses a group of compounds, including $\text{HOOC-CH}_2\text{-(R)Cgl-Aze-Pab-H}$ (in which Cgl represents cyclohexylglycine, Aze represents *S*-azetidine-2-carboxylic acid and Pab-H represents 4-aminomethyl-amidinobenzene), which is also
25 known as melagatran (see Example 1 of WO 94/29336). International Patent Application WO 97/23499 discloses prodrugs of *inter alia* melagatran.

None of the above-mentioned documents disclose or suggest the administration of an active thrombin inhibitor in conjunction with a prodrug of that thrombin inhibitor, or indeed in conjunction with a prodrug of any thrombin inhibitor.

5

Deep venous thrombosis (DVT) and pulmonary embolism (PE) are major health problems, which may give rise to serious outcomes. In particular, PE may be fatal, or may result in the development of pulmonary hypertension and heart failure from recurrent embolism. DVT may result in post-thrombotic venous insufficiency and ulcers in the affected part of the body (e.g. leg). Both are common conditions, which have a great impact on worldwide healthcare costs.

There is a considerable incidence of DVT and PE following orthopaedic surgery. For example, in patients undergoing total hip replacement, the incidence of DVT in the absence of thromboprophylaxis may be as high as 45 to 57%. Further, the incidence of proximal DVT may be between 23 and 36%, and that of fatal PE, 0.34 to 6%. In patients undergoing total knee replacement in the absence of thromboprophylaxis, the postoperative incidence of DVT is between 40 and 84%, of proximal DVT is between 9 and 20%, and of fatal PE is between 0.2 and 0.7%. In patients undergoing general surgery in the absence of thromboprophylaxis, the postoperative incidence of DVT is about 25%. (Reference: Chest (1998) 114, 531S to 560S.)

25

Low-dose, subcutaneous (s.c.) unfractionated heparin is the most widely used current prophylactic treatment for venous thromboembolism resulting from orthopaedic and general surgery. The incidence of DVT after total

hip replacement has been shown to be reduced (see Chest reference above).

5 The use of low-molecular weight heparin (LMWH) in the prophylaxis of DVT following total hip and knee replacement operations has been shown to further the reduce incidence (when compared to low dose unfractionated heparin), without a concomitant increase in bleeding (see Chest reference above).

10 However, prolonged treatment with heparins has been shown to give rise to an increased risk of osteoporosis. Heparins may also give rise to "heparin-induced thrombocytopenia" (HIT), are dependent on the plasma level of the endogenous thrombin inhibitor, antithrombin, and do not inactivate clot-bound thrombin.

15

Oral anticoagulants, such as warfarin (a vitamin K antagonist), has also been shown to be effective in reducing DVT after major surgery (see Chest reference above). However, due to the risk of bleeding, and the need for frequent laboratory control, the use of this substance is generally reserved for high risk patients, and/or for long term use. Vitamin K
20 antagonists also demonstrate a notable risk of interaction with other drugs and certain foods, and their use requires monitoring of the patient's blood coagulation status.

25 Antiplatelet agents, such as aspirin, have been shown to have limited efficacy in preventing DVT (see Chest reference above).

Comparative clinical studies carried out during the course of total hip replacement operations have shown that subcutaneous administration of

the thrombin inhibitor hirudin is superior to unfractionated heparin and LMWH in reducing the frequency of total and proximal DVT with no corresponding increase in bleeding (see Eriksson *et al* in Lancet, 347, 635 (1996) and J. Bone Joint. Surg., Sep., 11 (1996)). However, hirudin is
5 expensive and has an immunogenic potential.

Thus, there is a need for effective treatments of thrombotic conditions such as DVT.

10 Disclosure of the Invention

We have found, surprisingly, that administration of a low molecular weight thrombin inhibitor in conjunction with a prodrug of a (or a prodrug of that) thrombin inhibitor gives rise to a notable anticoagulant effect.

15

According to a first aspect of the invention there is provided a kit of parts comprising components:

- (a) a pharmaceutical formulation including a low molecular weight thrombin inhibitor, or a pharmaceutically acceptable derivative thereof, in admixture with a pharmaceutically acceptable adjuvant,
20 diluent or carrier; and
 - (b) a pharmaceutical formulation including a prodrug of a low molecular weight thrombin inhibitor, or a pharmaceutically acceptable derivative of that prodrug, in admixture with a
25 pharmaceutically acceptable adjuvant, diluent or carrier,
- which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

It is preferred that the prodrug of component (b) is a prodrug of the active low molecular weight thrombin inhibitor of component (a).

According to a further aspect of the invention, there is provided a method
5 of making a kit of parts as defined herein, which method comprises bringing a component (a), as defined above, into association with a component (b), as defined above, thus rendering the two components suitable for administration in conjunction with each other.

- 10 By bringing the two components "into association with" each other, we include that components (a) and (b) may be:
- (i) provided as separate formulations (i.e. independently of one another), which are subsequently brought together for use in conjunction with each other in combination therapy; or
 - 15 (ii) packaged and presented together as separate components of a "combination pack" for use in conjunction with each other in combination therapy.

Thus, there is further provided a kit of parts comprising:

- 20 (1) one of components (a) and (b) as defined herein; together with
(2) instructions to use that component in conjunction with the other of the two components.

The kits of parts defined herein may comprise more than one formulation
25 including an appropriate quantity/dose of thrombin inhibitor, and/or more than one formulation including an appropriate quantity/dose of respective prodrug, in order to provide for repeat dosing. If more than one formulation (comprising thrombin inhibitor or prodrug) is present, such

formulations may be the same, or may be different in terms of the dose of thrombin inhibitor/prodrug, chemical composition and/or physical form.

A further aspect of the invention provides a method of treatment of a condition in which inhibition of thrombin is required or desired, which comprises administration of:

- (a) a pharmaceutical formulation including a low molecular weight thrombin inhibitor, or a pharmaceutically acceptable derivative thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier; in conjunction with
 - (b) a pharmaceutical formulation including a prodrug of a low molecular weight thrombin inhibitor, or a pharmaceutically acceptable derivative of that prodrug, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier, -
- to a patient suffering from, or susceptible to, such a condition.

For the avoidance of doubt, as used herein, the term "treatment" includes therapeutic and/or prophylactic treatment.

"Pharmaceutically acceptable derivatives" of thrombin inhibitors and prodrugs includes salts (e.g. pharmaceutically acceptable non-toxic organic or inorganic acid addition salts) and solvates. It will be appreciated that the term pharmaceutically acceptable derivatives of active thrombin inhibitors includes those derivatives that have the same biological function and/or activity as that thrombin inhibitor but, for the purposes of this invention, does not include prodrugs of that thrombin inhibitor.

By "administration in conjunction with", we include that respective formulations comprising thrombin inhibitor and/or prodrug are administered, sequentially, separately and/or simultaneously, over the course of treatment of the relevant condition, which condition may be acute or chronic. Preferably, the term includes that the two formulations are administered (optionally repeatedly) sufficiently closely in time for there to be a beneficial effect for the patient, that is greater, over the course of the treatment of the relevant condition, than if either of the two formulations are administered (optionally repeatedly) alone, in the absence of the other formulation, over the same course of treatment. Determination of whether a combination provides a greater beneficial effect in respect of, and over the course of treatment of, a particular condition, will depend upon the condition to be treated or prevented, but may be achieved routinely by the skilled person.

15

Thus, the term "in conjunction with" includes that one or other of the two formulations may be administered (optionally repeatedly) prior to, after, and/or at the same time as, administration with the other component. When used in this context, the terms "administered simultaneously" and "administered at the same time as" include that individual doses of thrombin inhibitor and prodrug are administered within 48 hours (e.g. 24 hours) of each other.

Components (a) and (b) as described herein may also be presented (i.e. formulated) as a combined preparation (i.e. presented as a single formulation including low molecular thrombin inhibitor and prodrug).

Thus, there is further provided a pharmaceutical formulation including a low molecular weight thrombin inhibitor (or a pharmaceutically acceptable

derivative thereof) and a prodrug of a low molecular weight thrombin inhibitor (or a pharmaceutically acceptable derivative of that prodrug), in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

- 5 The term "low molecular weight thrombin inhibitor" will be understood by those skilled in the art. The term may also be understood to include any composition of matter (e.g. chemical compound) which inhibits thrombin to an experimentally determinable degree in *in vivo* and/or in *in vitro* tests, and which possesses a molecular weight of below 2,000,
10 preferably below 1,000.

Preferred low molecular weight thrombin inhibitors include low molecular weight peptide-based, amino acid-based, and/or peptide analogue-based, thrombin inhibitors.

15

- The term "low molecular weight peptide-based, amino acid-based, and/or peptide analogue-based, thrombin inhibitors" will be well understood by one skilled in the art to include low molecular weight thrombin inhibitors with one to four peptide linkages, and includes those described in the review
20 paper by Claesson in Blood Coagul. Fibrin. (1994) 5, 411, as well as those disclosed in US Patent N° 4,346,078; International Patent Applications WO 93/11152, WO 93/18060, WO 93/05069, WO 94/20467, WO 94/29336, WO 95/35309, WO 95/23609, WO 96/03374, WO 96/06832, WO 96/06849, WO 96/25426, WO 96/32110, WO 97/01338, WO 97/02284,
25 WO 97/15190, WO 97/30708, WO 97/40024, WO 97/46577, WO 98/06740, WO 97/49404, WO 97/11693, WO 97/24135, WO 97/47299, WO 98/01422, WO 98/57932, WO 99/29664, WO 98/06741, WO 99/37668, WO 99/37611, WO 98/37075, WO 99/00371, WO 99/28297, WO 99/29670, WO 99/40072, WO 99/54313, WO 96/31504, WO

00/01704 and WO 00/08014; and European Patent Applications 648 780,
468 231, 559 046, 641 779, 185 390, 526 877, 542 525, 195 212, 362
002, 364 344, 530 167, 293 881, 686 642, 669 317, 601 459 and 623 596,
the disclosures in all of which documents are hereby incorporated by
5 reference.

Preferred low molecular weight peptide-based thrombin inhibitors include
HOOC-CH₂-(*R*)Cha-Pic-Nag-H (wherein Cha represents cyclohexylalanine,
Pic represents (*S*)-pipecolinic acid and Nag represents noragmatine; known
10 as inogatran; see International Patent Application WO 93/11152) and,
especially, HOOC-CH₂-(*R*)Cgl-Aze-Pab-H (known as melagatran; see above
and International Patent Application WO 94/29336).

The term "prodrug" of a low molecular weight thrombin inhibitor
15 includes any compound that, following oral or parenteral administration,
is metabolised *in vivo* to form a low molecular weight thrombin inhibitor
(as defined herein), in an experimentally-detectable amount, and within a
predetermined time (e.g. within a dosing interval of between 6 and 24
hours (i.e. once to four times daily)), following oral or parenteral
20 administration. Prodrugs of the thrombin inhibitor melagatran that may be
mentioned include those disclosed in international patent application WO
97/23499. Preferred prodrugs are those of the formula R¹O₂C-CH₂-
(*R*)Cgl-Aze-Pab-OH (see the list of abbreviations above or in WO
97/23499), wherein R¹ represents C₁₋₁₀ alkyl or benzyl, such as linear or
25 branched C₁₋₆ alkyl (e.g. C₁₋₄ alkyl, especially methyl, propyl and,
particularly, ethyl) and the OH group replaces one of the amidino
hydrogens in Pab.

The term "condition in which inhibition of thrombin is required or desired" will be understood by those skilled in the art to include the following:

- 5 The treatment and/or prophylaxis of thrombosis and hypercoagulability in blood and tissues of animals including man. It is known that hypercoagulability may lead to thrombo-embolic diseases. Conditions associated with hypercoagulability and thrombo-embolic diseases which may be mentioned include inherited or acquired activated protein C
- 10 resistance, such as the factor V-mutation (factor V Leiden), and inherited or acquired deficiencies in antithrombin III, protein C, protein S, heparin cofactor II. Other conditions known to be associated with hypercoagulability and thrombo-embolic disease include circulating antiphospholipid antibodies (Lupus anticoagulant), homocysteinemi,
- 15 heparin induced thrombocytopenia and defects in fibrinolysis.

The treatment of conditions where there is an undesirable excess of thrombin without signs of hypercoagulability, for example in neurodegenerative diseases such as Alzheimer's disease.

20

- Particular disease states which may be mentioned include the therapeutic and/or prophylactic treatment of venous thrombosis (e.g. DVT) and pulmonary embolism, arterial thrombosis (e.g. in myocardial infarction, unstable angina, thrombosis-based stroke and peripheral arterial
- 25 thrombosis) and systemic embolism usually from the atrium during arterial fibrillation or from the left ventricle after transmural myocardial infarction, or caused by congestive heart failure; prophylaxis of re-occlusion (ie thrombosis) after thrombolysis, percutaneous trans-luminal

angioplasty (PTA) and coronary bypass operations; the prevention of re-thrombosis after microsurgery and vascular surgery in general.

Further indications include the therapeutic and/or prophylactic treatment
5 of disseminated intravascular coagulation caused by bacteria, multiple
trauma, intoxication or any other mechanism; anticoagulant treatment
when blood is in contact with foreign surfaces in the body such as vascular
grafts, vascular stents, vascular catheters, mechanical and biological
prosthetic valves or any other medical device; and anticoagulant treatment
10 when blood is in contact with medical devices outside the body such as
during cardiovascular surgery using a heart-lung machine or in
haemodialysis; the therapeutic and/or prophylactic treatment of idiopathic
and adult respiratory distress syndrome, pulmonary fibrosis following
treatment with radiation or chemotherapy, septic shock, septicemia,
15 inflammatory responses, which include, but are not limited to, edema,
acute or chronic atherosclerosis such as coronary arterial disease, cerebral
arterial disease, peripheral arterial disease, reperfusion damage, and
restenosis after percutaneous trans-luminal angioplasty (PTA).

20 Preferred conditions include thrombosis, especially DVT, including distal
and proximal DVT. The present invention finds particular utility in the
prophylactic treatment of DVT resulting from surgery, such as
gastrointestinal, or orthopaedic, surgery (e.g. hip or knee replacement).
This includes DVT resulting from immobilisation after surgery.

25

In accordance with the invention, thrombin inhibitors, prodrugs of
thrombin inhibitors, and derivatives of either, may be administered orally,
intravenously, subcutaneously, buccally, rectally, dermally, nasally,
tracheally, bronchially, topically, by any other parenteral route, or *via*

inhalation, in the form of a pharmaceutical preparation comprising the thrombin inhibitor or prodrug in a pharmaceutically acceptable dosage form. Depending on the disorder, and the patient, to be treated, as well as the route of administration, the compositions may be administered at
5 varying doses.

Preferred modes of delivery are systemic. For melagatran and derivatives thereof, preferred modes of administration are parenteral, more preferably intravenous, and especially subcutaneous. For prodrugs of melagatran,
10 preferred modes of administration are oral.

In the therapeutic treatment of mammals, and especially humans, thrombin inhibitors, prodrugs of thrombin inhibitors, and derivatives of either will generally be administered as a pharmaceutical formulation in admixture
15 with a pharmaceutically acceptable adjuvant, diluent or carrier, which may be selected with due regard to the intended route of administration and standard pharmaceutical practice.

Suitable formulations for use in administering thrombin inhibitors are
20 known in the art, and include those known from US Patent N° 4,346,078; International Patent Applications WO 93/11152, WO 93/18060, WO 93/05069, WO 94/20467, WO 94/29336, WO 95/35309, WO 95/23609, WO 96/03374, WO 96/06832, WO 96/06849, WO 96/25426, WO 96/32110, WO 97/01338, WO 97/02284, WO 97/15190, WO 97/30708,
25 WO 97/40024, WO 97/46577, WO 98/06740, WO 97/49404, WO 97/11693, WO 97/24135, WO 97/47299, WO 98/01422, WO 98/57932, WO 99/29664, WO 98/06741, WO 99/37668, WO 99/37611, WO 98/37075, WO 99/00371, WO 99/28297, WO 99/29670, WO 99/40072, WO 99/54313, WO 96/31504, WO 00/01704 and WO 00/08014; and

European Patent Applications 648 780, 468 231, 559 046, 641 779, 185 390, 526 877, 542 525, 195 212, 362 002, 364 344, 530 167, 293 881, 686 642, 669 317, 601 459 and 623 596, the disclosures in all of which documents are hereby incorporated by reference.

5

Suitable formulations for use with melagatran, derivatives and prodrugs thereof are described in the literature, for example as described in *inter alia* international patent applications WO 94/29336, WO 96/14084, WO 96/16671, WO 97/23499, WO 97/39770, WO 97/45138, WO 98/16252, 10 WO 99/27912 and WO 99/27913, the disclosures in which documents are hereby incorporated by reference. Otherwise, the preparation of suitable formulations may be achieved non-inventively by the skilled person using routine techniques.

15 The amounts of thrombin inhibitor, prodrug, or derivative of either, in the formulation will depend on the severity of the condition, and on the patient, to be treated, as well as the compound(s) which is/are employed, but may be determined non-inventively by the skilled person.

20 Suitable doses of thrombin inhibitors, prodrugs and derivatives of either, in the therapeutic and/or prophylactic treatment of mammalian, especially human, patients may be determined routinely by the medical practitioner or other skilled person, and include the respective doses discussed in the prior art documents disclosing thrombin inhibitors that are mentioned 25 hereinbefore, the disclosures in which are hereby incorporated by reference.

In the case of melagatran, suitable doses of active compound, prodrugs and derivatives thereof, in the therapeutic and/or prophylactic treatment of

mammalian, especially human, patients include those which give a mean plasma concentration of up to 5 $\mu\text{mol/L}$, for example in the range 0.001 to 5 $\mu\text{mol/L}$ over the course of treatment of the relevant condition. Suitable doses may thus be in the range 0.1 mg once daily to 25 mg three times daily, and/or up to 100 mg infused parenterally over a 24 hour period, for melagatran, and in the range 0.1 mg once daily to 100 mg three times daily for prodrugs of melagatran including those specifically mentioned hereinbefore.

- 10 In any event, the physician, or the skilled person, will be able to determine the actual dosage which will be most suitable for an individual patient, which is likely to vary with the condition that is to be treated, as well as the age, weight, sex and response of the particular patient to be treated. The above-mentioned dosages are exemplary of the average case; there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

The sequence in which the formulations comprising thrombin inhibitor, and prodrug, may be administered (i.e. whether, and at what point, sequential, separate and/or simultaneous administration takes place) may be determined by the physician or skilled person. For example, the sequence may depend upon many factors that will be evident to the skilled person, such as whether, at any time during the course or period of treatment, one or other of the formulations cannot be administered to the patient for practical reasons (e.g. the patient is unconscious and thus unable to take an oral formulation comprising either thrombin inhibitor or prodrug).

16

For example, in the treatment of thrombosis (e.g. DVT) resulting from surgery, such as gastrointestinal, or orthopaedic, surgery, and when the active thrombin inhibitor is melagatran, it is preferred that the formulation comprising melagatran is administered parenterally within two days (e.g. within 24 hours) of surgery (either prior to or after surgery), and particularly immediately prior to (e.g. within 2 hours), and/or within up to 12 hours after, surgery (e.g. at least one hour after surgery), and thereafter for up to between 3 and 7 (e.g. between 0 and 2, such as between 1 and 2) days after that surgery, and that the formulation comprising prodrug is administered orally within 7 days following that surgery (preferably once administration of melagatran has been terminated) for up to e.g. between 11 and 40 days, preferably 9 days, more preferably up to 8 days.

The method described herein may have the advantage that, in the treatment of conditions in which inhibition of thrombin is required or desired, it may be more convenient for the physician and/or patient than, be more efficacious than, be less toxic than, have a broader range of activity than, be more potent than, produce fewer side effects than, or that it may have other useful pharmacological properties over, similar methods known in the prior art for the treatment of such conditions.

The invention is illustrated, but in no way limited, by the following example.

Example 1Clinical Trial - Melagatran and EtOOC-CH₂-(R)Cgl-Aze-Pab-OH
Combination Therapy

- 5 A controlled, randomised, parallel group, Swedish multi-centre pilot study was carried out. The study was open with regard to the drugs under evaluation but was blind for the patients, all personnel at the study sites, and for the person monitoring the experiments with regard to the doses of melagatran and the prodrug of melagatran, EtOOC-CH₂-(R)Cgl-Aze-Pab-
- 10 OH (P; see WO 97/23499).

Dalteparin (Fragmin®; Pharmacia-Upjohn) was used as a reference compound.

- 15 Patients scheduled for primary elective total hip or knee replacement were eligible for inclusion, and were randomly selected into one of three groups, each to receive different doses of melagatran and P, or dalteparin. In all, 135 patients were included in the study, of which 105 patients could be used for evaluation with respect to thromboembolic events using central
- 20 assessment of locally performed phlebograms.

- About 32 patients in each treatment group were evaluated according to the protocol. A stratified randomisation, by centre and type of surgery, was used to ensure that approximately equal numbers of patients were given
- 25 each of the drugs under evaluation at all participating centres (in all six centres were used) for both types of surgery (hip or knee). Each centre received study drugs in blocks of four, separately for hips and knees. Within each block, the order of the study drugs was randomised.

The following formulations were used in the study:

Melagatran – 5, 10 or 20 mg/mL in aqueous saline solution.

- 5 P - appropriate weight (see below) in a tablet also comprising 59 to 63 mg corn starch, 115 mg microcrystalline cellulose and 2 mg sodium stearyl fumarate.

The following doses of melagatran and P were used in the study:

10

Treatment A - s.c. melagatran (1 mg) b.i.d. for 2 days, followed by oral administration of P (6 mg) b.i.d. for 6 to 9 days.

- 15 Treatment B - s.c. melagatran (2 mg) b.i.d. for 2 days, followed by an oral administration of P (12 mg) b.i.d. for 6 to 9 days.

Treatment C - s.c. melagatran (4 mg) b.i.d. for 2 days, followed by an oral administration of P (24 mg) b.i.d. for 6 to 9 days.

- 20 The patients receiving melagatran and P received treatment on the day of surgery. The patient received the first injection after induction of anaesthesia immediately before surgery. For knee-patients, the pre-operative melagatran injection was given before tourniquets were applied. The second injection was given in the evening the same day. The patient
25 received one melagatran injection in the morning and one in the evening over the next 24 hours, until oral administration of P, twice daily, started. The first oral dose of P was always taken in the morning. Thus, the total treatment period was between 8 and 11 days.

19

Treatment D - dalteparin (Fragmin®): one s.c. injection of 5000 U during the evening of the day before surgery, continuing with one s.c. injection every evening over a treatment period of 8 to 11 days.

- 5 The plasma concentrations of melagatran were recorded.

The results of the trial, in terms of the frequencies of thromboembolism after hip or knee surgery, are tabulated below:

	Treatment A		Treatment B		Treatment C		Treatment D	
	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)
Outcome	6/29	21	6/24	25	4/24	16	5/27	19

10

These data show that a combination of subcutaneously administered melagatran and orally administered P is effective in preventing DVT after orthopaedic surgery.

Claims

1. A kit of parts comprising:

- 5 (a) a pharmaceutical formulation including a low molecular weight thrombin inhibitor, or a pharmaceutically acceptable derivative thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier; and
- (b) a pharmaceutical formulation including a prodrug of a low
10 molecular weight thrombin inhibitor, or a pharmaceutically acceptable derivative of that prodrug, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier,

which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

15

2. A kit of parts as claimed in Claim 1, wherein the prodrug of component (b) is a prodrug of the thrombin inhibitor of component (a).

3. A kit of parts as claimed in Claim 1 or Claim 2, wherein components
20 (a) and (b) are suitable for sequential, separate and/or simultaneous use in the treatment of a condition in which inhibition of thrombin is required or desired.

4. A kit of parts as claimed in Claim 3, wherein the condition is deep
25 venous thrombosis.

5. A kit of parts as claimed in any one of Claims 1 to 4, wherein the thrombin inhibitor is melagatran.

21

6. A kit of parts as claimed in Claim 5, wherein the prodrug is of the formula



wherein R^1 represents linear or branched C_{1-6} alkyl and the OH group
5 replaces one of the amidino hydrogens in Pab.

7. A kit of parts as claimed in Claim 6, wherein R^1 represents methyl, ethyl or propyl.

10 8. A kit of parts as claimed in any one of the preceding claims, wherein the formulation comprising thrombin inhibitor, or derivative thereof, is a parenteral formulation and that comprising the prodrug, or derivative thereof, is an oral formulation.

15 9. A method of making a kit of parts as defined in any one of Claims 1 to 8, which method comprises bringing a component (a) according to any one of Claims 1 to 8, into association with a component (b) according to any one of Claims 1 to 8, thus rendering the two components suitable for administration in conjunction with each other.

20

10. A kit of parts comprising:

(1) one of components (a) and (b) as defined in any one of Claims 1 to 8; together with

(2) instructions to use that component in conjunction with the other of the
25 two components.

11. A pharmaceutical formulation including a low molecular weight thrombin inhibitor (or a pharmaceutically acceptable derivative thereof) and a prodrug of a low molecular weight thrombin inhibitor (or a

pharmaceutically acceptable derivative of that prodrug), in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

12. A method of treatment of a condition in which inhibition of thrombin is required or desired, which comprises administration of:

- (a) a pharmaceutical formulation including a low molecular weight thrombin inhibitor, or a pharmaceutically acceptable derivative thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier; in conjunction with
 - (b) a pharmaceutical formulation including a prodrug of a low molecular weight thrombin inhibitor, or a pharmaceutically acceptable derivative of that prodrug, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier,
- to a patient suffering from, or susceptible to, such a condition.

15

13. A method as claimed in Claim 12 in which component (a) is administered prior to commencement of administration of component (b).

14. A method of treatment of a condition in which inhibition of thrombin is required or desired, which comprises administration of a formulation as defined in Claim 11 to a patient suffering from, or susceptible to, such a condition.

15. A method as claimed in any one of Claims 12 to 14, wherein the condition is deep venous thrombosis.

16. A method as claimed in Claim 15, wherein the thrombosis results from surgery.

23

17. A method as claimed in Claim 16, wherein the surgery is gastrointestinal surgery or orthopaedic surgery.

18. A method as claimed in Claim 16 or Claim 17, wherein component
5 (a) is administered parenterally prior to and/or after surgery and component (b) is administered orally following that surgery.

19. The use of a thrombin inhibitor, or a pharmaceutically acceptable derivative thereof, in the manufacture of a medicament for the treatment
10 or prophylaxis of a condition in which inhibition of thrombin is required or desired, which treatment or prophylaxis comprises administration of:

(a) a pharmaceutical formulation including a low molecular weight thrombin inhibitor, or a pharmaceutically acceptable derivative thereof, in admixture with a pharmaceutically acceptable adjuvant,
15 diluent or carrier; in conjunction with

(b) a pharmaceutical formulation including a prodrug of a low molecular weight thrombin inhibitor, or a pharmaceutically acceptable derivative of that prodrug, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier,
20 to a patient suffering from, or susceptible to, such a condition.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 00/00756

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 38/55, A61K 38/06, A61P 9/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Thromb Haemost, Volume 81, 1999, H. Ericsson et al, "Pharmacokinetics and Pharmacodynamics of Melagatran, a Novel Synthetic LMW Thrombin Inhibitor, in Patients with Acute DVT" page 358 - page 363 --	1-19
A	Journal of Thrombosis and Thrombolysis, Volume 6, 1998, Diane P. Ignasiak et al, "Effects of Intravenous Enoxaparin and Intravenous Inogatran in an Electrolytic Injury Model of Venous Thrombosis in the Dog" page 199 - page 206 --	1-19
A	WO 9616671 A1 (ASTRA AKTIEBOLAG), 6 June 1996 (06.06.96) --	1-19

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

21 August 2000

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 00/00756

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9723499 A1 (ASTRA AKTIEBOLAG), 3 July 1997 (03.07.97) -- -----	1-19

INTERNATIONAL SEARCH REPORT

Int. tional application No.
PCT/SE00/00756

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 12-18
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).:

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE00/00756

Claims 12-18 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/ Rule. 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT
Information on patent family members

08/05/00

International application No.

PCT/SE 00/00756

Patent document cited in search report			Publication date	Patent family member(s)		Publication date
WO	9616671	A1	06/06/96	AU	689994 B	09/04/98
				AU	4191596 A	19/06/96
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